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TOTAL HIP ARTHROPLASTY, OSTEOLYSIS AND CARDIOVASCULAR DISEASE IN PATIENTS WITH OSTEOARTHRITIS OF THE HIP

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Total hip arthroplasty, osteolysis and long-term cardiovascular disease in patients with osteoarthritis of the hip

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my Family and Friends

LIST OF SCIENTIFIC PAPERS

I. Gordon M, **Rysinska A**, Garland A, Rolfson O, Aspberg S, Eisler T, Garellick G, Stark A, Hailer NP, Sköldenberg O.
"Increased Long-Term Cardiovascular Risk After Total Hip Arthroplasty: A Nationwide Cohort Study."
Medicine (Baltimore) 2016 Feb;95(6):2662

II. **Rysinska A**, Sköldenberg O, Garland A, Rolfson O, Aspberg S, Eisler T, Garellick G, Stark A, Gordon M.
"Aseptic loosening after total hip arthroplasty and the risk of cardiovascular disease: A nested case-control study."
PLoS One. 2018 Nov 14; 13(11):e0204391

III. **Rysinska A**, Aspberg S, Hailer NP, Hallman D, Laurencikas E, Eisler T, Gordon M, Sköldenberg O.
"Asymptomatic Osteolysis as a Risk Factor for Cardiovascular Disease-A prospective observational cohort study."
Manuscript

IV. **Rysinska A**, Aspberg S, Hailer NP, Eisler T, Gordon M, Sköldenberg O.
"Cardiovascular and Inflammatory Markers in Patients with and without Periacetabular Osteolysis after Total Hip arthroplasty-A cross sectional study."
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

CDR Cause of Death Register

CI Confidence interval

CT Computed tomography

CVD Cardiovascular disease

ECG Electrocardiography

HR Hazard ratio

NPR Swedish National Patient Register

OA Osteoarthritis

RR Relative risk

SHAR Swedish Hip Arthroplasty Register

THA Total hip arthroplasty

ABSTRACT

The pathogenesis of OA and CVD is currently related to inflammatory processes. It is unknown how OA and its surgical treatment impact the cardiovascular system.

Hypotheses

We hypothesized that (1) THA patients more than 5 years after the index surgery have an increased risk for cardiovascular morbidity and mortality compared with the general population and (2) that late cardiovascular risk following THA may be mediated by the development of osteolysis and systemic inflammation. Furthermore, we hypothesized that patients with asymptomatic osteolysis after THA (3) are more likely to develop CVD and (4) have a higher burden of cardiovascular risk markers than patients without periacetabular osteolysis.

Aims of the studies

The general aim of this thesis was to investigate patients treated with THA due to OA and patients treated with THA who subsequently underwent revision surgery and the associated risk of cardiovascular morbidity and mortality. Further aims were to compare patients with and without periacetabular osteolysis regarding CVD and cardiovascular risk markers. The specific aims were as follows:

Paper I: to determine whether there is a late correlation between THA and cardiovascular events.

Paper II: to compare patients after revision surgery due to aseptic loosening of the implant to controls (patients not having revision surgery) regarding the risk for cardiovascular morbidity and mortality and the time to first event during the exposure period.

Paper III: to investigate whether THA patients with asymptomatic periacetabular osteolysis have an increased long-term risk of CVD compared to THA patients without osteolysis and the time to event.

Paper IV: to compare THA patients with and without periacetabular osteolysis regarding cardiovascular risk markers and electrocardiography findings.

Materials and methods/results

Paper I: This was a nationwide, matched cohort study with data on 91,527 OA patients who underwent surgical treatment. Data were obtained from the Swedish Hip Arthroplasty Register. A control cohort consisting of 270,688 patients from the general Swedish population was matched at a ratio of 1:3 to each case by sex, age, and residence. The mean

follow-up time was 10 years. Patients with surgically treated OA of the hip had an increased risk of cardiovascular morbidity and mortality many years after the operation compared with controls.

Paper II: This was a nationwide, nested, case-control study consisting of 14,430 patients undergoing cemented THA due to OA between the years 1992 and 2005. The case group consisted of 2,886 patients who underwent reoperation on the treated hip due to osteolysis or aseptic loosening at any time within five years after the index surgery. Each case was matched with four controls (11,544). Patients with OA who underwent THA and subsequently underwent revision surgery due to loosening had a higher risk of developing cardiovascular events than controls.

Paper III: This was an observational cohort study of 139 patients who underwent uncemented THA between 1992 and 2007. All patients were assessed by CT of the affected hip to sort patients into 2 groups, those with periacetabular osteolysis (cases=33) and those without periacetabular osteolysis (controls=106). There was a higher rate of CVD among THA patients with periacetabular osteolysis than among THA patients without periacetabular osteolysis but no statistically significant risk increase.

Paper IV: This was a cross-sectional study consisting of 108 patients who underwent THA (uncemented components) due to OA between 1992 and 2007. All patients were assessed by CT of the affected hip. Patients with periacetabular osteolysis constituted the cases (n=19) patients without periacetabular osteolysis (n=89) were selected as controls.(89) Markers of inflammation, risk markers for CVD and ECG abnormalities were collected and compared between the groups. There was no difference in the risk burden for CVD many years after THA between patients with and without periacetabular osteolysis.

Conclusions: Patients with surgically treated OA of the hip have an increased risk of cardiovascular morbidity and mortality many years after the operation. Patients who undergo revision surgery due to aseptic loosening and/or osteolysis have a higher risk of developing cardiovascular events. These observations may be indicative of common disease pathways. Furthermore, while the risk for CVD in patients with periacetabular osteolysis is slightly higher, there is no significant difference in the risk burden for CVD compared with patients without periacetabular osteolysis. The examination of a larger sample and the use of comparable durations after surgery are recommended.

SAMMANFATTNING PÅ SVENSKA

Total höftledplastik är en vanlig behandling för höftledsartros när konservativ behandling inte givit resultat. Långtidsuppföljning av hjärt-kärlsjukdom efter total höftledsplastik har tidigare ej varit föremål för vetenskapliga studier. Det är heller inte klarlagt hur artros och dess kirurgiska behandling påverkar det kardiovaskulära systemet. Den främsta orsaken till omoperation på lång sikt efter en höftplastik-operation är osteolys. Orsaken till osteolys är inte säkert klarlagd men den dominerande hypotesen är att slitageprodukter från de konstgjorda materialen leder till en låggradig inflammation i vävnaden runt protesdelarna vilket leder till lossning av desamma. En omoperation pga osteolys är ofta omfattande och riskfylld. Aterosklerotisk hjärtkärlsjukdom betraktas också som en inflammatorisk sjukdom med låggradig inflammation i kärlväggen till följd av åderförfettning. Det kan finnas ett samband mellan dessa tillstånd, t ex genom att osteolys stimulerar den inflammatoriska processen i blodkärlen och på så vis bidrar till utveckling och progress av ateroskleros. En annan förklaring skulle kunna vara att patienter som både har osteolys och ateroskleros har en benägenhet att utveckla inflammation i flera organsystem.

Vårt syfte med följande studier var att undersöka möjliga samband mellan operation för osteoartros med total höftledsplastik, osteolys efter denna operation och senare risk för hjärtkärlsjukdom.

Målet för delarbete I var att undersöka om total höftledsplastik pga artros ökar långtidsrisken för hjärtkärlsjukdom och död. Efter 9 till 13 års uppföljning hade gruppen som erhållit höftprotes högre risk för död i hjärtkärlsjukdom, de hade också en högre andel återinläggningar på sjukhus till följd av hjärtkärlsjukdom.

I delarbete II jämförde vi patienter som blivit omopererade pga peracetabulär osteolys inom fem år efter operation med total höftledsplastik med en kontrollgrupp som erhållit höftprotes men ej blivit omopererade. Vi jämförde förekomst av hjärtkärlsjuklighet samt tiden till första hjärtkärlhändelse. Det visade sig att patienter som genomgått en omoperation pga aseptisk lossning/osteolys hade högre risk än förväntat att drabbas av hjärtkärlsjukdom jämfört med patienter som ej opererats för aseptisk lossning.

I delarbete III och IV jämförde vi patienter med periacetabulär osteolys med patienter som ej hade periacetabulär osteolys. Alla patienter hade genomgått total höftledsplastik pga osteoartros mellan 1992 och 2007. Samtliga undersöktes med skiktröntgen för att påvisa förekomst av osteolys. Vi jämförde antalet hjärtkärlhändelser samt tiden till första hjärtkärlhändelse mellan grupperna. Vidare undersökte vi halter av högsensitivt CRP, vita

blodkroppar samt blodfetter vilka har visat sig vara prediktorer för hjärtkärlsjukdom. Samtliga patienter undersöktes även med EKG då vissa EKG-förändringar kan förutsäga ökad risk för hjärtkärlsjukdom. Vi kunde inte visa några statistiskt signifikanta skillnader mellan grupperna.

I sammanfattning visar studierna på en association mellan total höftledsplastik och senare risk för kardiovaskulär sjukdom och död under långtidsuppföljning samt också en koppling till högre risk för hjärtkärlsjukdom hos patienter som genomgått omoperation på grund av osteolys/lossning av den konstgjorda ledpannan än för patienter som inte är omopererade. Däremot fann vi ingen koppling mellan osteolys och kardiovaskular sjukdom eller riskmarkörer för kardiovaskulär sjukdom hos en mindre grupp patienter med osteolys efter total höftledsplastik jämfört med patienter utan osteolys efter höftprotes-operation. Hur kopplingen mellan total höftledsplastik, osteolys och hjärtkärlsjukdom ser ut och eventuellt kan förklaras återstår att visa.

BACKGROUND OSTEOARTHRITIS

OA is a degenerative, progressive joint disease that leads to the degradation of cartilage and subchondral bone. The word *osteoarthritis* is derived from the Greek:

osteo meaning “of the bone”

arthro meaning “joint”

itis meaning “inflammation”

Epidemiology

OA occurs mostly later in life and tends to be slowly progressive. It is by far the largest reason of pain in working-age population (1) and in the elderly.(2, 3) Knees, hips, and hands are normally affected. Prevalence ranges between 12% (4) to 22%.(5) From the age of 40 onwards, the risk of developing OA increases.(6) The incidence and prevalence are higher in developed countries.(7) Pain and disability are the main symptoms. For the individual, mobility and activities of daily living are reduced and in addition; discomfort, low self-worth, and loneliness.

Risk factors

There are risk factors, increasing the risk of developing OA.(8) They are mainly as follows: sex, age, obesity, diet, joint injury, and occupation.

Sex: Women have a higher risk of developing OA in the hand, foot, and knee.(9) The increased incidence is shown at the time of menopause, and this has led to hypotheses regarding the role of estrogen. The results of other studies are inconsistent, and the difference could be ascribed to other factors, such as bone strength.(10, 11)

Age: One of the main prognosticators of OA is age.(12) The mechanism that leads to the increased prevalence and incidence is not fully understood. It is probably a combination of multifactorial changes, including weakening of muscles, thinning of cartilage, biological changes, and decreased proprioception.(13, 14)

Obesity: With increases in prevalence worldwide, there are also reasonable indications that obesity is one of the most extensive risk factors for OA in not only the knee but also the hand and hip, with a dose-response gradient with increasing BMI.(15, 16) The risk increases by 35% for every 5-unit increase in BMI and is higher in women than in men. The association between hip OA and high BMI is weaker but still present.(17) Bilateral, but not unilateral, disease in the hip is clearly associated with being overweight. Hand OA is associated with

obesity.(18) The impact of obesity may not just be biomechanical but may also be associated with metabolic syndrome (19) and inflammatory systemic effects.

Diet: Nutritional factors may have an influence on the development of OA through a variety of mechanisms. Many laboratory and observational studies confirm this feasibility. High dietary intake of micronutrient antioxidants may protect against tissue damage and could theoretically protect against OA. The Framingham Knee OA Cohort study found that persons with a low vitamin C intake had an enlarged risk for developing radiographic and painful OA.(20) Bone metabolism is reliant on on the presence of vitamin D.(21) Low levels of vitamin D in tissues can promote the process of OA. The Framingham study reported an increased risk for the progression of radiographic OA in patients with a low intake of vitamin D.(22) Reversely, the Framingham study mentioned above reported no evidence that high antioxidant intake reduces the incidence of knee OA.(20)

Joint injury: Injuries are commonly associated with damage to the cartilage, subchondral bone. Tibial plateau fracture leads to radiological evidence of post-traumatic OA in 25%-45% of cases on long-term follow-up.(23-25) Malalignment of the joint has also been shown to promote the progression of OA.(26)

Occupational: Repetitive joint movements have been correlated with an increased risk of OA. Individuals in occupations requiring squatting or kneeling have twice the risk of developing knee OA than those in professions not requiring any physical activity. Hip OA has also been associated with standing for a long time and lifting.(27)

Pathophysiology

OA is a slow process of remodeling cartilage and sub articular bone(28). Development takes typically many years. The disease is characterized by degenerative structural changes in joint-osteophyte formation, laxity of ligaments, weakening of muscles surrounding the joint and low-grade synovial inflammation. Several attempts have been made to clinically and radiographically define OA; not rarely with low levels of agreement between them.(29) The cartilage undergoes degradation, bone remodels by responding actively to the inflammatory process in surrounding tissues. Increased activity of several cytokines and chemokines (30) in the joints, drive production of enzymes that mediate destruction of cartilage.

Diagnosis

The diagnosis of OA is dependent on clinical and radiological features. Patient´s history and clinical examinations of the affected joint together with plain radiographs is crucial.

Pain, stiffness and disability are clinical symptoms. OA on plain radiographs is characterized by reduction of joint space, presence of osteophytes, subchondral cysts and subchondral sclerosis, **(Figure 1)**. Early painful OA may not have radiographic changes, and conversely, patients with severe radiographic signs may be entirely without symptoms. The association existing between severity of OA signs on radiographs and clinical symptoms is not strong.(29)

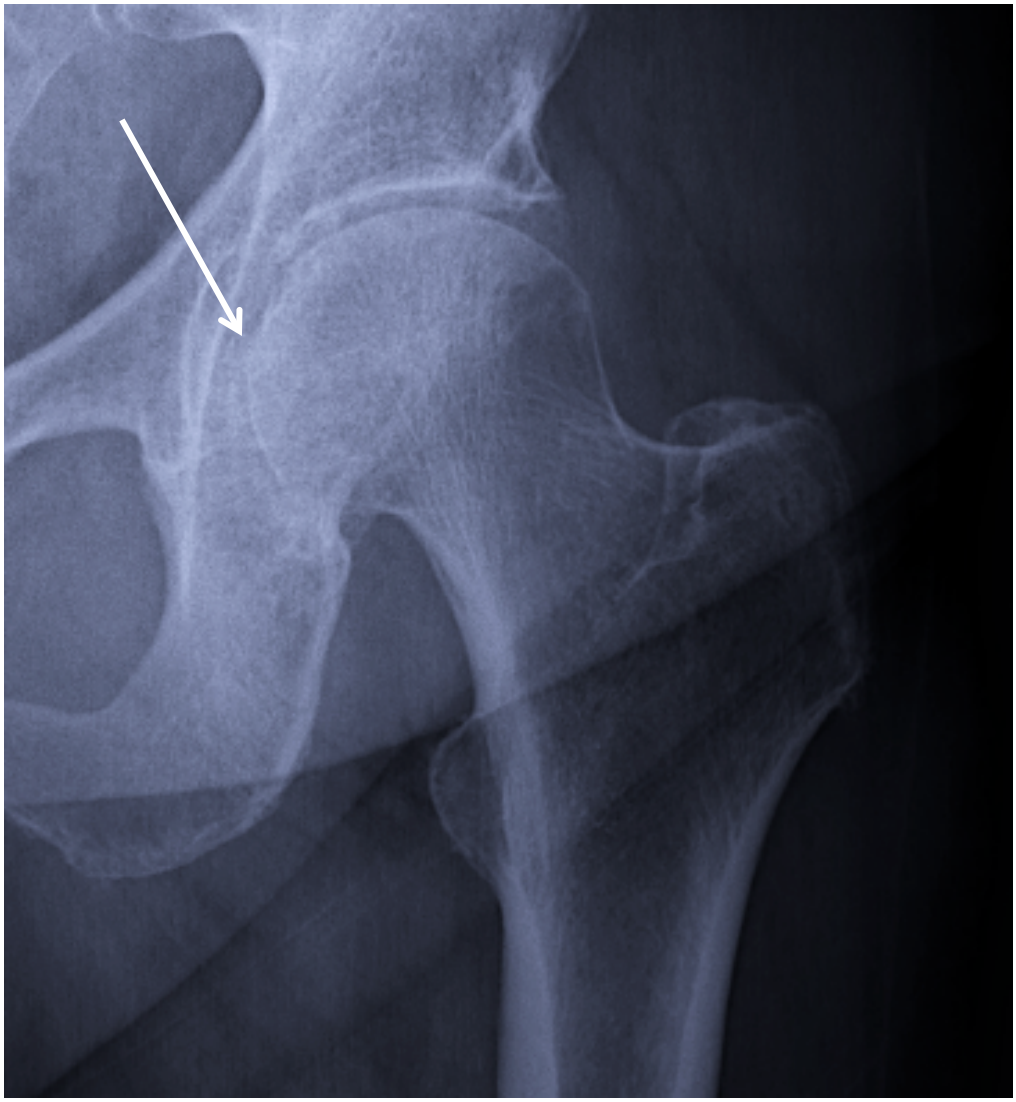

Figure 1. Early osteoarthritis of the hip.

Treatment

Conservative therapy should always be initiated—analgesics, physiotherapy, ambulatory aids and weight loss. The surgical indication for hip replacement requires severe pain in the affected joint, loss of function, physical findings on examination and the presence of OA on radiographs. The surgery aims to replace the degenerated joint surfaces, with an artificial joint, i.e., total hip arthroplasty (THA),**(Figure 2)**.

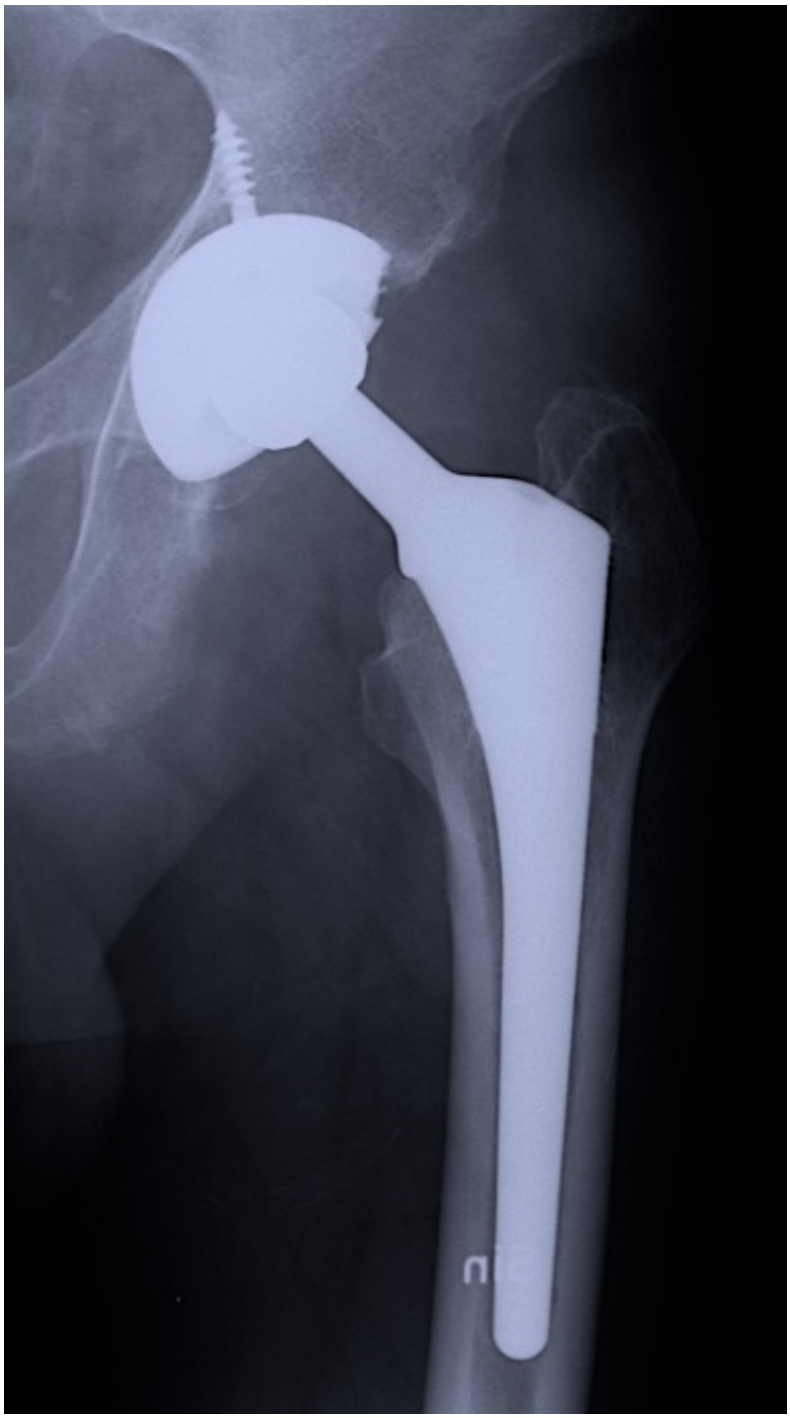

Figure 2. THA, uncemented components.

The term “arthroplasty” is derived from two Greek words: (a) *“arthro”*, meaning joint, and (b) *“plastikos”*, associated with moulding.(31)

- Painful OA is the main indication for THA. Other indications are as follows:
- Rheumatoid arthritis.
- Post-traumatic OA due to previous hip injury or fracture.
- Avascular necrosis of the femoral head. May occur after injury. It is also associated with long-term use of steroid medications and excessive alcohol intake.
- Developmental dysplasia of the hip, also called hip dysplasia. It is a congenital condition of disturbed development. It ranges between minor laxities of the hip to a complete dislocation of the joint. Children are treated, but painful OA in this patient group is common in adulthood.
- Displaced femoral neck fractures in some patient groups, depending on age, previous mobility, etc.

TOTAL HIP ARTHROPLASTY

History

Joint pathology has been identified as OA in ancient skeletons, with a prevalence and distribution seemingly similar to those of today. Roman(32), Mediaeval and Saxon(33) populations with OA have been found on archaeological excavations in Britain. Surgeons have been searching for more than two hundred years to find a treatment for the painful condition that OA can become,(34) and treatment has evolved from joint excision and osteotomy to modern THA. At the end of the eighteenth century, removal of the femoral head was practiced for many joint diseases. Anthony White (1782-1849) performed the first excision arthroplasty in 1821 in London. Patients still had some mobility but lacked stability.(35) Other surgical attempts made to treat OA have included arthrodesis of the joint, osteotomy,(36) nerve division, calcium deposition and joint lavage. There was a broad search for materials that could be used to resurface or even replace the hip joint. Professor Themistocles Glück presented the first recorded trial of hip replacement at the 10th International Medical Conference in Germany in 1891. Ivory was used to replace the femoral heads of 14 patients whose joints were destroyed by tuberculosis.(37) All patients suffered later from chronic infection; subsequently, Glück declared that joint infection is a contraindication to joint replacement. In Czechoslovakia, the surgeon Vitezlav Chlumsky (1867-1943) started experiments with interpositional materials to replace the worn joint surfaces. Silver plates, rubber struts, magnesium, zinc and other materials were used. Other tested materials included skin, fascia lata and even pig bladder submucosa. The materials were placed between the articulating surfaces of the hip. The first mould arthroplasty was performed with glass in 1925, formulated by the American surgeon Marius Smith-Petersen. The prosthesis consisted of a hollow hemisphere that could conform over the femoral head and provide a clear surface for movement. Although glass is a biocompatible material, it did not have the strength to resist the forces going through the hip joint and crushed. Bone resorption, soft tissue reactions and aseptic loosening were the main problems. In 1936, two metallurgists, Charles Venable and Walter Stuck, fabricated a cobalt-chromium alloy, subsequently named vitallium. It was promptly applied in orthopaedics; the alloy was strong and resistant to corrosion, and it has been used in various prostheses since. The metal turned out to be a success, but the resurfacing technique was still not satisfactory. The hunt for better materials and ways to fix the prostheses continued. Smith-Peterson and Wiles were the forerunners of a new era of arthroplasty in 1938, when the first prosthetic total hip replacement procedure was performed.(38) A reshaped femoral head covered by a vitallium

cup composed the interposition. During these early years, different groups tested a plethora of materials, varying from stainless steel and cobalt to rubber, glass, and even ivory.(36) Mechanical failure and catastrophic complications were common due to poor designs and inferior materials. In Paris, two brothers (Judet) tried to replace the painful arthritic hip surfaces with an acrylic material "borrowed" as a material from dentists. The acrylic had a blank surface, but disastrously became loose. Efforts were made to fix the cup to the bone, which improved the results, leading to an early form of the modern solution of fixing the cup to the bone. In 1942, Austin T. Moore from South Carolina designed a replacement for the entire femoral head. Primarily, it was used to treat femoral neck fractures, but it was also used in some cases of OA. This kind of hip replacement, named hemiarthroplasty, only addressed the damaged articular surface of the femoral head. The worn-out surface of the acetabular cartilage was not restored. The prosthesis consisted of two pieces; one metal ball that was fit into the acetabulum and a metal stem that was inserted into the proximal femur. Due to the still arthritic destruction of the acetabulum, the results were not acceptable. There was still no sufficient technique for fixing the femoral stem to the bone; many patients suffered from pain due to loosening of the implant. In 1947, the Judet brothers designed an acrylic femoral head prosthesis made of polymethylmethacrylate (PMMA). This material is still used today but as bone cement, not as an articular surface due to the high risk of femoral neck fracture. The first metal-on-metal (MoM) prosthesis was used by the English surgeon George McKee. In 1953, the Thompson stem was used with a new one-piece cobalt-chrome socket as the new artificial acetabulum. In the 1960s, Sir John Charnley introduced and revolutionized the management of the arthritic hip. He contributed to the evolution of total hip replacement in three ways: 1) presenting the idea of low-friction torque arthroplasty; 2) fixing the components to the upper end of the femoral shaft with acrylic cement; and 3) introducing a high-density polyethylene (PE) cup cemented into the drilled-out acetabulum as a bearing material.(39) This method was defined and named "low-friction arthroplasty". Periprosthetic joint infection is a disastrous complication; Charnley constructed a filtered air enclosure in the operating theatre with special suits for the team to address this complication. The infection rate decreased dramatically. Reports of implant survivorship showed 81% and 77% at the 25-year follow-up.(40, 41) Charnley and colleagues are responsible for the understanding of modern THA advancing from a salvage procedure with poor long-term outcomes to one of the best and most frequently used elective surgeries. The technique used today does not differ dramatically from the one he described. In 1991, THA was named "the operation of the century".(42)

Epidemiology

Over 1.5 million THA procedures are performed every year worldwide.(39) This represents a milestone in orthopaedic surgery. THA is an effective surgical treatment for relieving hip pain and improving physical function caused by OA. The results are excellent, and the treatment is generally regarded as the standard procedure when physiotherapy and non-surgical treatment have failed. The main objective for THA is to relieve pain, improve function and provide a higher quality of life for the individual. Worldwide, 1.7 million THA procedures were performed in 2013.(43) The number is expected to grow; between 2005 and 2010, the number of THA procedures increased by 16%.(44) The amount of primary THA procedures in the US is likely to grow by 174% between 2005 and 2030 (572,000 surgeries per year).(45) In Sweden, the incidence of these surgeries is also growing steadily. In 2018 in Sweden, 18,629 patients underwent primary THA (46), **(Figure 3)**. One natural explanation for the growing incidence could be the longer life expectancy, and thus the increasing number of elderly people. There are complications after THA, and they can simply be divided into early and late. Some, such as dislocation, deep joint infection and usually periprosthetic fracture, require surgical treatment. Thromboembolism, nerve injury, leg length discrepancy and heterotopic ossification are treated non-surgically.

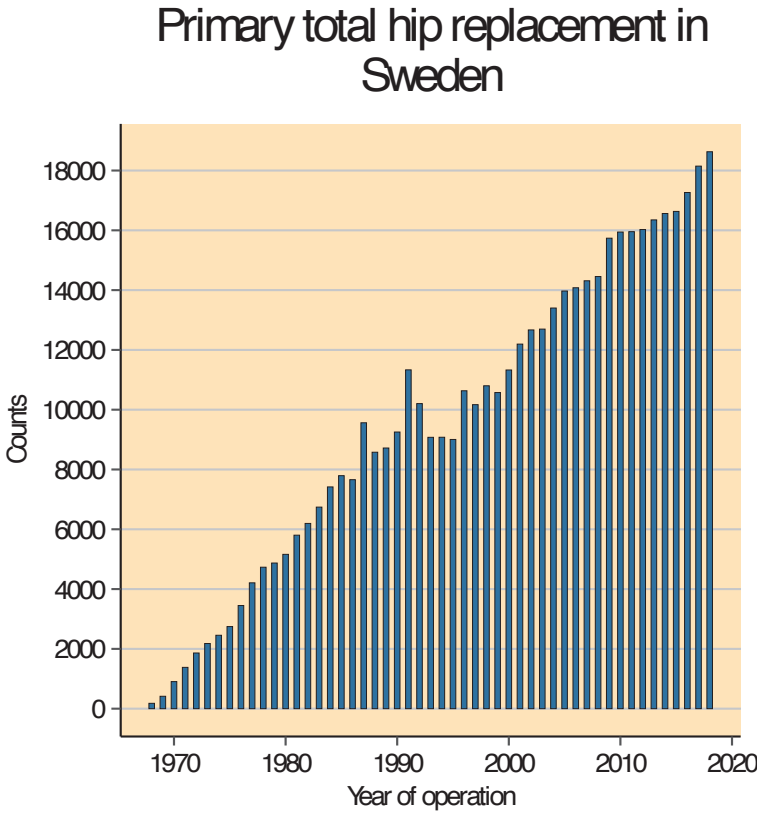

Figure 3. Incidence of THA in Sweden 1970-2018. Reprinted with permission from the SHAR.

Arthroplasty registries

The National Registry Committee in France, 1995, defined a registry as *"a continuous and exhaustive collection of nominative data about one or more health-related events in a geographically defined population, by a team having specific expertise, to be used for research and public health studies"*.(47) Data on patient implants are systematically collected for all THA procedures in Sweden performed in both private and public hospitals. Sex, age, diagnosis, surgical technique and date of surgery are recorded. Revision surgery is used as an endpoint. Only "revision surgery" is used to classify prosthesis as having "not survived". The definition of "revision surgery" by the Swedish Hip Arthroplasty Register (SHAR) is quite exact: "any surgical procedure during which one or more prosthesis components are replaced, removed or added". This makes it possible to analyse the complications in detail. Centrally collected and analysed data can offer a rapid understanding of when used products lead to complications. Additionally, it is possible to find the affected individuals and quickly withdraw the products from the market. The essential method to estimate the results of surgery is Kaplan-Meier survival analysis with revision surgery as the endpoint; therefore, implants must be connected to individual patients, and it is vital to be able to plot survival curves. The two most common reasons for revision surgery are aseptic loosening and infection, **(Figure 4)**. In some countries that do not permit individual connections to implants, outcomes are presented as the rate of revisions per 100 component years. Registries provide data not only for epidemiological and demographic studies but also for comparisons of outcomes of different kinds of implants and clinics within a country. Revision surgery and the decision to perform surgery in individual cases depend on many factors that are of the utmost most importance to the patient's health status. Patients may thus have complications postoperatively without undergoing revision surgery due to high risk or other reasons. Therefore, using revision surgery as the only endpoint is problematic. Patient-reported outcome measures; (PROM) include evaluations of pain, function, quality of life and patient satisfaction are collected in line with those of the survival analysis to further assess the results of hip replacement.

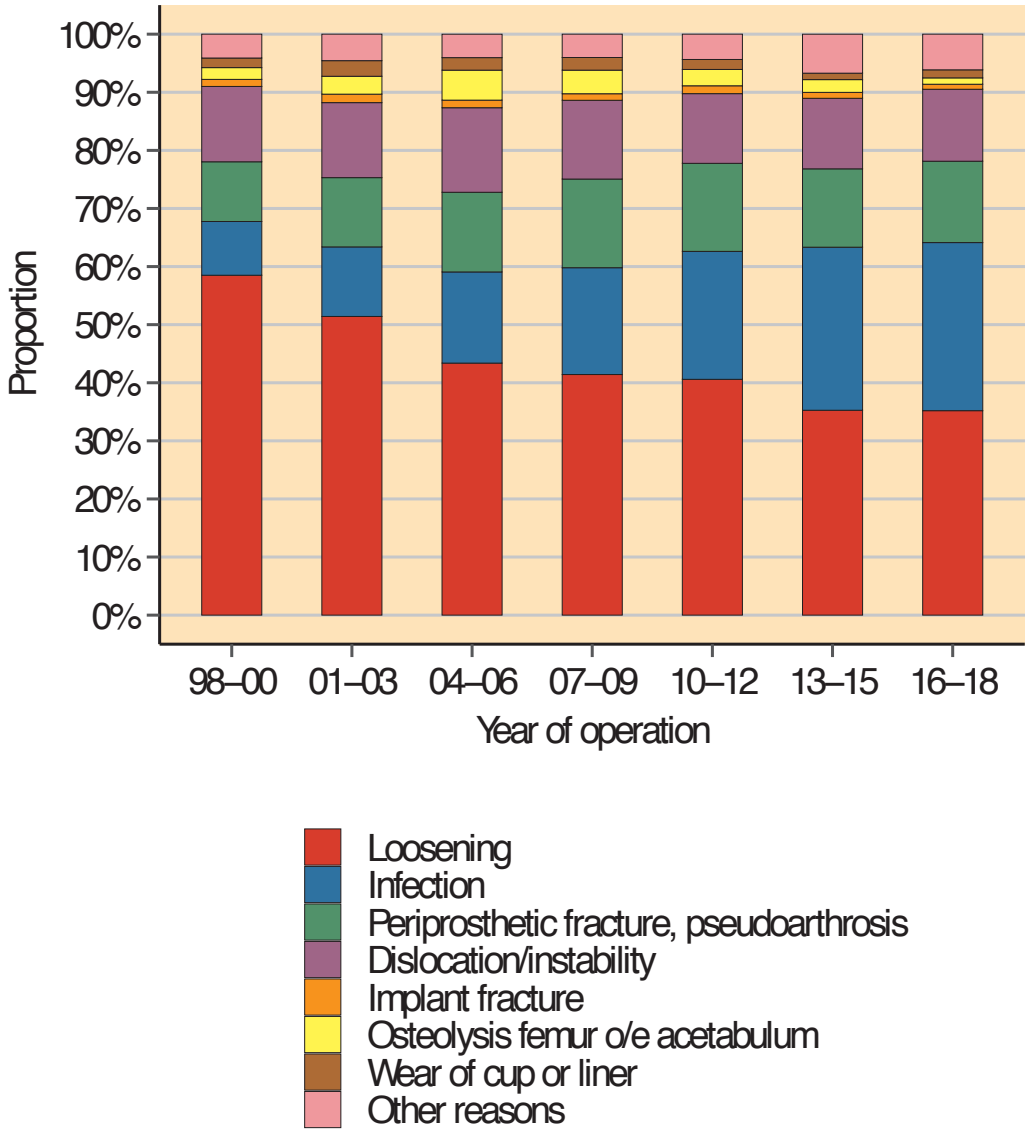

Figure 4. Reasons for reoperation in Sweden 1998-2018. Reprinted with permission from SHAR.

Components and materials

A standard THA typically consists of four individual components, **(Figure 5)**. The stem is the part of the prosthesis that is inserted into the proximal femur. The proximal part (top end) of the femoral stem is called the trunnion. It is taper shaped, for the femoral head to wedge onto. The femoral head is held in place on the trunnion with friction. The femoral head, which can be in different diameters, fits into the analogue size of the cup. The cup is inserted into the acetabulum. Types of arthroplasty are usually referred to methods of fixation, cemented or uncemented**.** In Sweden (46), the cemented technique is the most common. The cement creates an interlocking fit between the implant and the bone. Uncemented implants have surface features considered to bone ingrowth (48) and biological fixation over time.

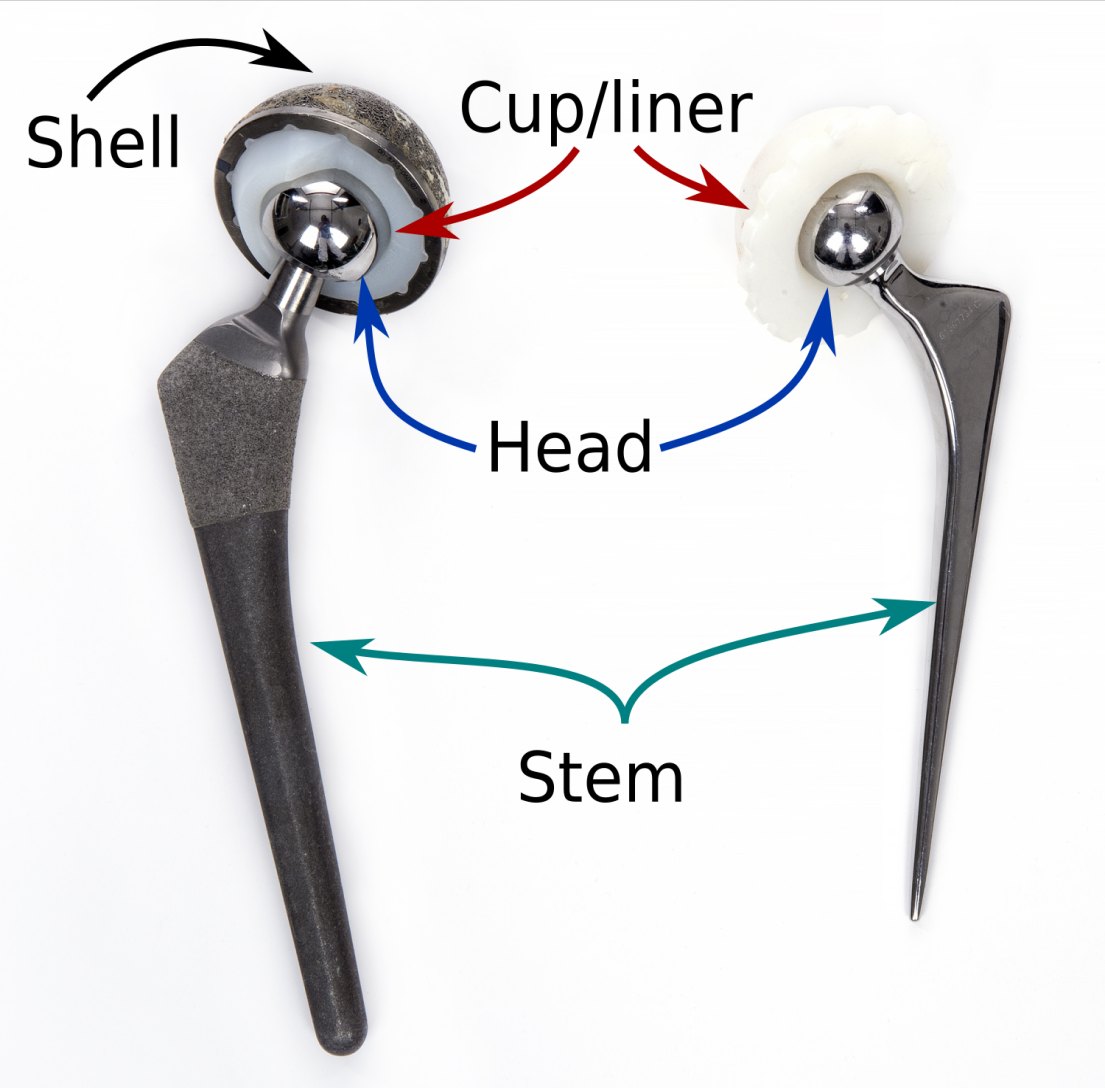

Figure 5. THA components. Uncemented on the left, cemented on the right.

Materials commonly used in THA

Metallic alloys

The most common alloys used in implant components are stainless steel, cobalt-chromium alloy, and titanium alloy. The materials must keep high strength, elasticity, ductility, and resistance from corrosion, and biocompatibility.

Polyethylene

Polyethylene (PE) is a widely used material in hip replacement liners, and the introduction of highly crosslinked PE (HXLPE) in THA has been one of the most important improvements since introduction in the late 1990s. The purpose was to reduce wear-induced periprosthetic osteolysis and loosening. It is created by radiation and reheating PE, which induces cross-linking between PE molecules. During cross-linking free radicals are formed, resulting in making the HXLPE exposed to oxidative degradation and material embrittlement. To diminish this process the antioxidant vitamin E may be added to the PE, which binds to free radicals and by this diminishes the oxidation process and wear. The change to HXLPE in acetabular liners has contributed to a dramatic reduction in wear compared to PE.(49-51)

Ceramic materials were introduced in THA in the 90´s to address the problem of PE wear (52) due to it´s high resistance to scratch. Ceramics is neither a metal, nor a semiconductor or a polymer. The problem with older ceramic implants was development of cracks that could lead to implant failing abruptly by fracturing.(53) Modern ceramics show fewer complications with failure.(54)

Bearings

Bearing materials in articulating surfaces of the hip prosthesis may consist of PE, metal or ceramic. The surfaces should have a low production of wear particles and low coefficient of friction. The most common used articulations are combinations of a hard metal or ceramic head and a soft liner of PE-"hard-on soft articulation". Metal-on-PE (MoP) or ceramic-on-PE (CoP) are the most used materials in THA articulations in Sweden. "Hard-on-hard" articular combinations consist either of metal-on-metal (MoM) or ceramic-on-ceramic (CoC). MoM bearings showed improved wear features in the 1990s, resulting in 35% of all bearings used in the US in the early 2000s. A growing failure rate was observed in joint registries in 2010s (55, 56) A comprehensive amount of clinical situations from small tissue lesions to large bone destructions were reported describing periprosthetic tissue infiltration by inflammatory cells (57), necrosis and metallic debris. The condition has many labels such as; aseptic lymphocytic vasculitis-associated lesions (ALVAL) metallosis (58), and pseudotumours.(59, 60) Clinical symptoms are pain, due to tissue damage; possible loosening of implants which eventually may lead to revision surgery. Besides local reactions, metal ions in serum have been linked with systemic responses and toxic effects on organs are reported.(61) There is no definition of safety levels of metal ions in serum regarding the potential toxic accumulation of metal products in organs. CoC bearings show low wear rates not only due to the materials hardness but also because of a reduced inflammatory tissue reaction from wear particles released. Disadvantades with the bearing include fracture of the material and squeaking.(62)

Cement and fixation

"Bone cement" is extensively used for the fixation of implants in various orthopaedic and trauma surgeries. It was developed in the late 1950s. The real substance is PMMA, which is an acrylic polymer formed by mixing two sterile components: a powder and a liquid. The powder consists of the cement (acrylic) polymer together with an initiator (di-benzoyl peroxide). A radio-opacifier (zirconium oxide or barium sulphate) is added for visibility on X-ray, and an antibiotic is usually added. It is the viscosity of the cement that enables manipulation of the cement during the surgery. It has the function of grout between the cancellous bone and the implant Heat is generated due to an exothermic reaction. The cement has no adhesive effects, so it does not live up to the definition of cement, i.e., "a substance that bonds two things together". Although the chemical composition of bone cement has essentially remained the same over the years, the cementation technique has changed,

which has significantly improved the results.(63) The cement has the role of space filler, creating a close-fitting mechanical interlock holding the implant to the irregular bone surface. Thus, there is no adhesive bond attachment between the bone and the prosthesis. Thermal and chemical damage to the bone during the cementation process leads to formation of granulation tissue and an interface created between bone and the cement. The cementing technique is good to use in osteoporotic bone and antibiotics can be added as prophylaxis to reduce the risk of postoperative infection. The cement cures quickly which enables rapid patient rehabilitation. In rare cases, peroperative during cement implantation cement in its liquid phase can enter the bloodstream before curing and cause bone cement implantation syndrome (BCIS).(64) There is no consensus regarding definition of the condition, which includes hypoxia, (65)hypotension, (66) cardiac arrhythmia, (67) increased pulmonary vascular resistance and cardiac arrest.(68)

Cementless fixation

Due to the problems with wear and loosening an alternative to uncemented implants was introduced in the late 1970s. Cementless components were designed to grant sufficient initial stability. The technique used to fix a cementless prosthesis is called press fitting. The implants are inserted with physical force on the prosthetic part so the maximal press-fit to the peri-implant host bone can be obtained. Once the implant is stabilized in the bone, the components allow the physiological transmission of biomechanical forces through the joint. The surface of the prosthesis is rough and/or has a porous coating allowing close bony juxtaposition. Initial research was performed to find a coating capable of enhancing bone ingrowth, i.e., osseointegration. This term thus describes the direct structural and functional connection between living bone and the surface of a load-bearing artificial implant, (69) with load bearing as defined by Albrektsson.(70) Bone formation is initiated around the prosthesis due to a series of biological events. Early postoperatively there is micromotion between the implant and the bone; an interface is formed between bone and the implant. With time peri-implant bone remodels according to the man made new biomechanical situation, the implant surface is replaced by new bone.(71-73) Hydroxyapatite is currently the most frequent used material on uncemented implants due to its similarity and biocompatibility to bone.(74)

Problem of wear

Wear is the result when damage or removal occurs of material from one or both of two solid surfaces under loading in moving contact, followed by the release of particles. There are different types of wear: adhesive wear, abrasive wear, third body wear and linear wear. In

adhesive wear, the weaker surface of the two opposing surfaces transfers onto the stronger and harder surface. Abrasive wear develops when rough areas on the surface of the stronger material form grooves in the softer surface or if free particles (cement, bone, metal or PE) are embedded between two bearing surfaces during motion. Linear wear is defined as the degree of penetration of the prosthetic head into the PE liner. Despite the material or design, artificial joints generate particles due to wear and the biological activity is highly dependent on the characteristics and quantity of wear particles. All by-products from currently used implants cause an inflammatory response to a greater or lesser degree (75, 76), which involves macrophages in particular, as well as fibroblasts, lymphocytes and osteoclasts. Type, size and density of material change the host's overall cell and tissue response.(77) PE particles range in size from 0.1 to 10 μm, and those between 0.1 and 0.5 μm are suggested to be most biologically active. The wear rate per year in mm of PE is associated with the development of osteolysis and its volume.(78, 79)

Osteolysis

Osteolysis happens when resorption of peri-implant bone occurs. It is a common and serious complication of THA on the long term.(80) Bone tissue undergoes lifelong continuous turnover and remodeling.(81) The constant ongoing process involves osteoclasts removing-resorption, and osteoblasts rebuilding (82) bone-ossification. If imbalance happens in the process of bone turnover and osteoblast activity increases it may lead to bone resorption, peri-implant osteolysis and subsequent aseptic loosening. If pressure in the joint space increases, the wear particles migrate out to spaces with lower pressure and diffuse from the peri-implant area into tissues around the joint.(77) Joint fluid containing particles is driven out to new periprosthetic areas and therefore drives the total spread of osteolysis and increases both peri-implant bone resorption and bone stock weakening.(83) The destruction of peri-implant bone tissue is progressive and loosening may subsequently occur.(84) Initially radiolucent lines and/or cavitation in the periprosthetic bone interface (85) can be detected on radiographs as insular areas of bone resorption. Willert and Semlitsch were the first presenting the theory of aseptic loosening of cemented implants as a result of wear by particles.(86) It was initially called "cement disease". Later it was named "particle disease" by Dr William Harris.(87) The osteolytic lesion can develop in diverse forms in the peri-implant bone tissue, and can develop into large volumes. As long as the implant is stable there are no clinical symptoms, early symptoms of a loose and unstable implant may present as pain in groin and buttock. As the osteolysis progress subluxation and dislocation may occur. Several classification schemes have been proposed to describe periacetabular osteolysis and bone loss in revision THA.(88-

90) The Paprosky classification is a comprehensive and widely used, due anatomical orientation on the location and amount of bone loss, it is used as treatment recommendation when surgery is indicated. Surgery is associated with high patient morbidity and mortality.(80)

Imaging modalities

Radiographic methods are essential in assessing osteolysis. Consecutive radiographs are needed to detect and measure advancement. Initially the osteolytic lesions on plain radiographs are hard to detect. Therefor computed tomography (CT) is a more precise method to evaluate the extension of the peri-implant osteolysis regarding the location, implant position, volume and amount of bone loss, **(Figure 6)**. Various descriptions have been made to describe and define periacetabular osteolysis on CT (91, 92) and there is still no consensus. Definition of periacetabular osteolysis in this project was defined as a defect with loss of bone trabeculae in direct connection to the surface of the acetabular component and its volume was measured in $cm^{3.}$ Magnetic resonance imaging (MRI) offers a higher soft tissue contrast than radiography and CT. Soft tissue conditions not detected by plain radiographs and CT may be visualized by MRI, and clarify failure.(93) Several methods have been developed to assess PE wear.(94, 95) To evaluate prosthetic movement and potential failure of implant consecutive radiographs are compared with three-dimensional measures using image-processing software. Radiostereometric analysis (RSA) developed in 1970s by Selvik et al. is considered the most precise method to detect relative changes over time in implant position.(96) It not only evaluates implant stability but also wear of the PE liner. Peroperatively small tantalum beads are embedded in the periprosthetic bone. Their position used as a reference can discover movements of the prosthetic components.

Figure 6. CT image of uncemented THA, periacetabular osteolysis.

CARDIOVASCULAR DISEASE

CVD relates to the circulatory system, which includes the heart and blood vessels. Cardiovascular events refer to any vascular incident that causes damage to the heart muscle. CVD comprises many types of conditions; some of them might develop at the same time or lead to other conditions or diseases in the group. The major CVD are as follows:

- Coronary heart disease (disease of the coronary arteries supplying the heart)
- Cerebrovascular (disease affecting arteries supplying the brain)
- Peripheral arterial disease (disease of the arteries supplying the extremities)

Epidemiology

CVD is by far the largest cause of death globally, causing an expected number of 17.9 million deaths every year. In 2016, 31% of all global deaths were represented by CVD. Of these deaths, 85% were due to myocardial infarction and stroke. One-third of these deaths occur in people younger than 70 years of age. Over 75% of CVD-related deaths occur in low- and middle-income countries.(97) CVD can be avoided by changing and reducing behavioural risk factors, including the use of tobacco, unhealthy diet/obesity, and a lack of physical inactivity.(98) Risk factors for CVD are several. Patients affected by hypertension, diabetes mellitus, and hyperlipidaemia) should receive treatment to prevent CVD and premature death. It is also known that addition of CVD risk factors alters the vascular risk.(99)

Pathophysiology

The process of atherosclerosis is characterized by progressive thickening and hardening of large and medium-sized arteries and is most often a consequence of lipid deposits in the inner lining of the artery, called the intima layer. It is characterized by vascular obstruction from lipid deposits, which results in reduced blood flow. Previously, it was considered of as a disorder of age and cholesterol. Currently; it is seen as the result of a multifaceted interaction between inflammation and lipids. Atherosclerosis is the most common cause of CVD; it starts with the development of atherosclerotic plaques. Atherogenesis mainly occurs in the inner layer of arteries called the intima, especially where arteries divide. High levels of total cholesterol, low-density lipoprotein (LDL) and triglycerides and low levels of high-density lipoprotein cholesterol have been associated with CVD morbidity and mortality in many studies.(100, 101)

Cardiovascular disease and inflammation

LDL particles cause atherosclerosis. The endothelium exposed to accumulate LDL particles is a major element of disease initiation and progression.(102) Accumulated LDL particles in the intima undergo modifications rendering them pro-inflammatory (103) and immunogenic features. There are several cells driving plaque inflammation, including immune cells, smooth muscle cells, platelets, and endothelial cells. Monocytes penetrate the endothelial barrier, and inflammatory processes induce the differentiation of monocytes into mature macrophages. Macrophages phagocytose LDL and become laden with lipids, which give them a foamy appearance. The fatty deposits on the inside of the blood vessel wall recruit monocytes. They accumulate in the intima and become foam cells. These cells play an important role at all stages of atherosclerotic lesion development. The maintenance of foam cells and the secretion of cytokines cause the later formation and progression of plaque leading to a narrowed artery lumen. Subsequently, foam cells undergo apoptosis or necrosis, leaving their lipid-rich content in the walls of the arteries. This contributes to the formation of atherosclerotic plaques. Destabilization and rupture of atherosclerotic plaque may lead to acute coronary syndromes, and is the typical cause of coronary arteries that causes myocardial infarction.(104)

AIMS

Paper I

The aim of this study was to determine whether there is an increased risk of late cardiovascular mortality and morbidity after THA surgery.

Paper II

The aim of this study was to determine whether there is an increased risk of cardiovascular mortality and morbidity in patients after revision surgery due to aseptic implant loosening (cases) compared with patients after THA without revision surgery (controls).

Paper III

The aim of this study was to investigate whether THA patients with asymptomatic periacetabular osteolysis have an increased long-term risk of CVD compared to THA patients without osteolysis and to assess the time to event.

Paper IV

The aim of the study was to compare THA patients with and without periacetabular osteolysis regarding cardiovascular risk markers and electrocardiography (ECG) findings.

PATIENTS AND METHODS

Paper I

Study design: a nationwide matched cohort study. Cases were recruited from the SHAR, including only patients who underwent cemented THA due to primary OA. Patients treated with rarely used implants (occurring <300 times per year in the SHAR) were excluded. Each case was matched with 3 random controls that were not present in the SHAR through Statistics Sweden's registry of the total population. Controls were matched to the arthroplasty cohort by sex, age ± 5 years, and residence. Residence was defined as municipality, except for the 3 largest cities (Stockholm, Malmö, and Gothenburg), where the municipality was subdivided into parishes. The matching criteria were chosen to limit socioeconomic confounding. All register data were matched with their unique Swedish personal identity numbers. Exposure was THA survival of longer than 5 years. The primary outcome was cardiovascular mortality after 5 years. Secondary outcomes were total mortality and re-admission due to cardiovascular events.

Paper II

Study design: a nationwide, nested, case-control study. Cases were defined as any patient who had undergone reoperation of the treated hip due to aseptic loosening at any time point. Each case was matched 4 to 1 with patients from the SHAR. The controls had the same exposure time for cardiovascular events, which were only included during that exposure period. Subjects with an exposure time of less than 6 years were excluded from the study. The study population consisted of patients who had undergone THA due to primary OA between 1992 and 2005. Only patients treated with cemented THA with metal-on-PE bearings were included. The cups used in THA in the study population consisted of standard PE (in Sweden, HXLPE was introduced in 2005). Both modular and non-modular necks were used. The exposure period was defined as the period between 5 years after the first surgery and 1 year before the first reoperation due to aseptic loosening. Follow-up data on death, causes of death, admission to inpatient care, reasons for inpatient care admission and reoperation were collected until 2012. Only the first hip was included for patients who underwent bilateral surgery.

Paper III

Study design: an observational cohort study. Patients who underwent uncemented THA with metal-on-PE articulation performed due to primary OA were included. Only one hip (the first treated hip) was included in patients treated with bilateral surgery. All patients underwent THA between 1992 and 2007 due to OA; cases had asymptomatic periacetabular osteolysis, and controls had no osteolysis. The minimum follow-up time was 10 years due to the slow development of osteolysis. The inclusion period lasted from 2012 to 2017. To determine the presence of periacetabular osteolysis, CT of the hip region was performed at the inclusion visit. Follow-up data after their primary surgery on CVD and causes of death were collected until April 2019, a minimum of 12 years. The exclusion criteria were as follows: pain from the hip (visual analogue scale) [VAS] score ≥3, with 0 indicating no pain and 10 indicating extreme pain), any hip surgery after the primary surgery, ever use of bisphosphonates and inflammatory arthritis.

Paper IV

In this cross-sectional study, patients who underwent uncemented THA due to OA were included. Cases with asymptomatic periacetabular osteolysis after uncemented THA and their controls (without periacetabular osteolysis) were compared regarding risk markers for CVD and inflammation. The patients included were operated on between 1992 and 2007. The presence of periacetabular osteolysis was determined at the inclusion visit by CT between 2012 and 2017. Biochemical variables were total leukocytes, high-sensitivity C-reactive protein (hs-CRP) and lipids. Blood specimens and ECG data were collected at inclusion. All patients had metal-on-PE bearings. Only the first hip was included for patients treated with bilateral surgery. The exclusion criterion was pain from the hip (VAS score ≥3, with 0 indicating no pain and 10 indicating extreme pain). Patients treated with revision surgery due to periacetabular aseptic loosening were also excluded.

Data collection

SHAR

The SHAR was founded in 1979 and provides prospective, observational, nationwide data on hip arthroplasty.(105) It is the second oldest arthroplasty quality register in the world, with the overall aim of improving hip arthroplasty care in Sweden. Individual patient data, such as age, sex, diagnosis, surgical approach and type of implant, are collected. Since 1992, personal identity numbers have been collected, allowing for patient-specific follow-up, with a coverage of 97%, and capturing 98% of all patients treated with THA at all Swedish hospitals. One of many important features is that all revision surgeries are collected and registered, which makes it possible to investigate complications in detail.

Statistics Sweden

Statistics Sweden is a government agency responsible for coordinating the system for official statistics. It provides statistics on the Swedish population for decision-making, debate and research. According to the law, the statistics must be official for the public, investigation and research. Statistics Sweden started in 1968 and comprises detailed information on all individuals' demographics and places of residence, as well as the population size, changes in the population, including births, deaths, immigration, and emigration, and sex, age, civil status, country of birth and citizenship. It develops, produces and distributes statistics not only to the government and its agencies but also to the public. The statistics have to be objective and available to the public; they are divided into 22 subjects and 112 statistical areas.

Cause of death register

The cause of death register has existed since 1952 and is a high-quality, nearly complete register of all deaths in Sweden. It can be linked to other national registers and therefore is an important foundation of information for medical research and official statistics.

Study designs

Cohort studies

Cohort studies are observational, and participants are only observed, without any intervention. They are especially appropriate to study rare exposures or exposures for which randomization is not possible for practical or ethical reasons. The aim of a cohort study is to select study participants who are as similar as possible with the exception of their exposure status. Some part of the cohort is exposed to a specific risk factor, and the other part is not. All participants must be free of the outcome under investigation and have the potential to develop the outcome during the study period. It is a longitudinal type of study; research participants are followed over a period of time, often many years. All participants share a common characteristic, for example, demographic similarity. The incidence of disease in the exposed group is compared with the incidence in the unexposed group. The relative risk is used to assess whether the exposure and disease are causally linked. This makes it possible to analyse the impact of the exposure and helps to understand what factors increase or decrease the likelihood of developing disease. Cohort studies can be performed retrospectively and prospectively. In a retrospective cohort study, the exposure and outcome have already occurred; therefore, it is less time consuming and costs less. However, if exposure occurred long ago, adequate data on exposure might be problematic to collect due to recall bias. The data available are not designed with the thought of the study in mind, which may lower the quality of the study. The advantages of cohort studies are numerous. A cohort study may consist of a large number of participants who can be followed, and it is possible to draw conclusions regarding the association between risk factors and the disease outcome. Cohort studies are particularly useful at identifying timelines over which exposures can contribute to the disease. Participants are free from disease in the beginning of the study; therefore, cohort studies are particularly useful for identifying timelines over which exposures can contribute to the disease.

Collecting prospective data in a large group of participants for a long time is complicated, time consuming and expensive. Participants may drop out or change behaviour due to awareness of being part of a study cohort. Confounding variables in a large-scale study make the data analysis complex. It can therefore be challenging to relate cause and effect.

Case-Control studies

In case-control studies, two groups are defined at the start: one with the outcome of interest/disease (cases) and one without the outcome/disease (controls). The selection of cases should be based on objective inclusion and exclusion criteria from a reliable source, such as a disease registry. The controls must be at a similar risk of developing the outcome as the cases. Matching controls to cases reduces the effects of confounders, which are variables associated with exposure and potentially causes of the outcome. A comparison is performed retrospectively to assess whether there is a statistically significant difference in the rate of exposure to the risk factor defined in the study between the groups. No intervention is undertaken to change the development of the disease. The exposure is determined from each of the two groups of individuals. The studies are designed to estimate odds. This study design is useful for studying rare conditions or diseases. Studies may be performed with relatively few cases. The performance of the study is less time consuming because the condition or disease has already occurred. Findings can be obtained relatively quickly. The study design allows for the simultaneous observation of multiple risk factors and the establishment of an association. The data quality may be lower because it relies on people's memory (recall bias). One problem with selecting cases is that some of those with the disease/outcome may not have a formal diagnosis, may not show up for medical care, may be misdiagnosed or may have died before getting a diagnosis. Cases and controls should be as similar as possible except for their outcome/disease status. An association found between an exposure and a disease does not necessarily mean that one factor caused the other.

Cross-sectional studies

Cross-sectional studies are performed to assess the presence or absence of a disease/outcome and the presence of absence of an exposure at a specific point of time. The design is a type of observational study without any intervention done. In case-control studies participants are selected based on the outcome status, and in cohort studies participants are selected on the exposure status. In cross sectional studies the participants are selected based on inclusion and exclusion criteria set just for the study to assess the exposure and the outcomes without the need of follow-up. It can be used for surveys and to assess the prevalence of diseases/outcomes in clinic-based samples. Conduction and performance of cross-sectional studies can be made relatively fast and inexpensive. However due to it´s one-time measurement it is difficult to derive casual relationship from cross sectional studies.

Statistical methods

Survival analysis

Survival analysis is the analysis of time-to-event data and comprises a whole set of tests, graphs and models that are used in different study design situations. Data are described as the length of time from the time origin to an endpoint of interest. The time origin must be defined in a way such that individuals are as similar as possible in terms of the level of disease, for example, at the time of diagnosis or surgery. The endpoint, or the event of interest, is also supposed to be well defined. The length of time from the time origin to the endpoint is calculated. Different objectives of survival analysis include determining patterns of event times, comparing distributions of survival times in different groups of individuals, and examining factors affecting the risk of an event of interest occurring. All survival analyses test how predictive variables predict an outcome variable that measures the time until an event. Basic concepts are important in any time-to-event analysis, including censoring, survival and hazard functions.

Censoring

If the event or outcome of interest does not occur within the study period, the individual will be censored, and this may occur due to loss to follow-up or a different event that makes follow-up impossible. This type of censoring is called right censoring, while censoring due to events or hazards that happened before the time origin is called left censoring.
Survival and hazard functions: two probabilities are used to describe survival data, i.e., the probability of survival and the probability of the hazard. The survival probability is also called the survivor function and is the probability that an individual survives from the time origin to the endpoint from a hazard/diagnosis. The hazard probability focuses on the probability that an individual suffers from an event during a length of time considering time in small intervals.

Kaplan-Meier estimation

Kaplan-Meier analysis is a method for describing survival graphically and mathematically. Three assumptions are used in Kaplan-Meier analysis. The first is that at any time, patients who are censored have the same survival prediction as those who continue to be followed. The second assumption is that survival probabilities are the same for individuals enrolled early and late in the study. The third is that the event occurs within the stated time frame. The survival probability at any particular time is calculated by the following formula: for each time interval, the survival probability is calculated as the number of individuals surviving

divided by the number of patients at risk at each time point. It is also possible to compare survival between two or more groups. The method is not suitable to analyse the impact of predictors on survival.

Cox proportional hazards regression model

To study how several predictors impact survival, regression analysis is required. The Cox proportional hazards regression model assesses the association between predictors and survival time between two or more groups and is by far the most common model used to compare survival. The model also allows the examination of how specified factors impact the rate of a particular event at a particular point in time. This rate is commonly referred to as the hazard rate. Variables in a Cox regression are named predictors, covariates or independent variables; all three expressions have the same meaning.

Poisson regression

Poisson regression is a regression model to predict the outcome as the dependent variable and a count of events occurring during a given timeframe or space. The count has to have a Poisson distribution, meaning that the mean and variance should be the same.

Log-rank test

The log-rank test a test to assess whether there are any significant differences in survival times between groups being studied and to compare all events occurring at all time points on the survival curve. It takes the whole follow-up period into account. Neither the shape of the survival curve nor the distribution of survival times is required to compare the survival of groups. The same assumptions are used in the log-rank test as in the Kaplan-Meier survival analysis. It detects a difference between compared groups when the risk of an event happening is consistently larger for one group than another.

Chi-squared test

The chi-square test is a statistical hypothesis test designed to analyse categorical data comparing two or more proportions from independent groups. The test can also be used to test the association between two nominal variables, or one nominal and one ordinal. For small samples, Fisher's exact test is used.

T-test

The t-test is a type of hypothesis test to determine whether there is a significant difference between the means of two groups, which are related in some features. Three key values are needed to calculate a t-test. They are the standard deviation of each group, the mean difference between the data sets and the number of values in each group.

Mann-Whitney U test

When the assumption of a normal distribution is not met, non-parametric tests should be used for hypothesis testing. The Mann-Whitney U test compares the distribution of two independent ordinal variables. It is similar to the t-test but without the assumption of a normal distribution. It is not sensitive to outliers because it is designed to use the median and not the mean. Because the test uses the median, it works on subjects' rank order in the overall distribution instead of their deviance from the mean or the differences between the means of the two groups.

Table of statistical tests used

	Study I	Study II	Study III	Study IV
Survival analysis	X	X		
Kaplan-Meier estimation			X	
Cox Proportional hazard regression	X		X	
Poisson regression		X		
Log-rank test			X	
Chi-squared test			X	X
T-test				X
Mann-Whitney U test				X

RESULTS

Paper I

The THA cohort had a lower cardiovascular mortality risk the first 5 to 9 years after surgery than the control cohort, the hazard ratio was 0.94 (95% CI 0.89-0.98). After 8.8 years the risk increased in the THA cohort, and was higher. Between 9 and 13 years after surgery, the hazard ratio was 1.11 (95% CI 1.05-1.17). Furthermore, patients from the THA cohort were admitted at a higher frequency to the hospital due to cardiovascular events than the controls, with a risk ratio of 1.08 (95% CI 1.06-1.11).

Paper II

Patients who had who had surgery for implant loosening after THA due to osteoarthritis had a higher risk of cardiovascular morbidity than controls. The risk increase was primarily caused by cardiac events. Mean follow-up time was 9.8 years, and the longest follow-up time was 19.8 years. At 5, 7.5 and 10 years after surgery, 88.3%, 79.5% and 68.9% were still alive. The control group had a higher comorbidity burden, but after adjusting for possible confounders, cases had an approximately 50% increased relative risk of cardiac events.

Paper III

Patients with periacetabular osteolysis had a higher rate of CVD than controls up to 27 years after surgery. The female sex was borderline protective against CVD and atherosclerotic disease in the crude analysis but lost statistical significance after adjustment. After adjusting for different follow-up times with a longer follow up time among cases and for possible confounders, we found a 60% increase in risk, but this increase was not statistically significant.

Paper IV

No differences were found in cardiovascular risk markers or ECG abnormalities between THA patients with and without periacetabular osteolysis at a mean follow-up time of 17.7 and 11.8 years after the primary surgery. Additionally, no differences were found in comorbidities, including CVD, with the exception of atrial fibrillation being borderline statistically significant. Cases had a longer follow-up time than controls.

DISCUSSION

Study I

In this nationwide cohort study, we found an increased risk of long-term mortality and morbidity in patients surgically treated for OA of the hip compared with controls. This effect was mainly ssociated to an increased risk of CVD and an increased risk of hospital admission due to cardiovascular events. The results indicate an association of hips surgically treated for OA with CVD, an association that, at least to our knowledge, has not been described before. More recent studies have shown improved survival in patients after THA compared to patients in a matched population.(106, 107)

Study II

In this nationwide, nested, case-control study, THA patients after revision surgery due to osteolysis and/or implant loosening had a higher risk of cardiovascular morbidity than controls, primarily driven by cardiac events. The control group had a higher burden of comorbidities, but after adjusting for possible confounders, there was an approximately 50% increase in the relative risk of cardiac events in the case group. Few studies have been performed in this particular field, but an American study has shown (108) that among patients with failed THA, obesity is independently associated with early primary THA failure due to aseptic loosening. Obesity is also both an independent risk factor and a risk marker for the development of coronary artery disease, heart failure and atrial fibrillation.(109) In addition, atrial fibrillation is strongly correlated with inflammation.(110)

Study III

Patients with periacetabular osteolysis had a higher rate of CVD than controls up to 27 years after surgery, but with CVD occurring among cases later in the observation period. This was despite the fact that they were on average younger and healthier at the time of primary THA surgery, as reflected by a higher proportion of controls being in ASA class 3 at surgery as well as a higher proportion of controls with preoperative CVD events. After adjusting for different follow-up times and confounders, we found a 60% increase in risk, but this increase was not statistically significant.

Study IV

In this cross-sectional study, we could not find any differences in cardiovascular risk markers or ECG abnormalities between THA patients with and without periacetabular osteolysis. The

mean follow-up time after the primary surgery was 17.7 years in the osteolysis group and 11.8 years in the non-osteolysis group. We also failed to find any differences in comorbidities, including CVD, with the exception of atrial fibrillation, which was borderline statistically significant.

Strengths and limitations

Strengths of studies I+II

This is a large-scale population-based cohort with a long follow-up (21 years) of THA. Another strength is the increased relative risk among patients despite both self-selection and surgeon-selection bias, which means that medically unfit patients will, to a lower degree, be inclined for surgery. Health care registers in Sweden are of high quality and offer excellent opportunities for epidemiological research. Both the SHAR and Swedish National Patient Register (NPR) have good accuracy and completeness.(111) Swedish personal identity numbers allow us to identify and link data to the administrative system from where we collected the data regarding the cardiovascular diagnoses investigated in this study and death dates, which allows patients to be followed throughout the study period until an event, death or emigration. All death dates in Sweden are contained in the Swedish cause of death register. Unknown deaths occur for patients moving permanently abroad, but it is unlikely that many patients would emigrate at an advanced age. To our knowledge, the risk analysis of cardiovascular admission to inpatient care among THA patients has only rarely been previously investigated. The findings in the current study are consistent with those previously reported. In addition, the findings presented in the current study are consistent with previously reported rates of hospital admission due to cardiovascular reasons in THA patients and matched controls.

Limitations of studies I+II

No adjustments for obesity and smoking were performed. Obesity is associated with an increased risk for OA, CVD and atrial fibrillation. There are ICD codes for obesity, but rarely used; due to this uncertainty underdiagnosed obesity is still a limitation of the study. Smoking is a risk factor for CVD, and there are no data on smoking habits. Lung cancer was used as a proxy for comparing smoking in our cohorts, but there was no evidence of greater smoking habits in the THA group. Hip OA is often treated with NSAID, both before and after surgery, the class of drugs is known to increase the risk of CVD.The increased risk of cardiovascular mortality and morbidity could be mediated through NSAID. Intake of

NSAID could explain some of the overrepresentation of cardiovascular morbidity in the THA group, but controlling for this factor is not possible. Medically unfit patients for revision surgery were not identified, resulting in possible misclassification bias and/or immortal bias. If included, the effect size would rather decrease than increase because they were too sick for undergoing revision surgery and would due to this incorrectly be classified as controls. Patients with pain in a previously well-functioning THA may be more prone to contact healthcare, and be diagnosed with other conditions, such as CVD. This could have increased the effect estimate for the case group. Primary outcome definition was stringent; admission due to cardiovascular event had to be at least 2 days to be classified as a cardiovascular event. This reduced detection bias reduced as en passant registration of cardiovascular diagnoses occurs. It was also minimized by including one year before revision surgery to eliminate possible preoperative CVD diagnosis in cases with osteolysis/aseptic loosening.

Strengths of studies III+IV

This was, to our knowledge, the first study determining asymptomatic THA patients with periacetabular osteolysis and comparing them with THA controls regarding CVD, cardiovascular risk markers and inflammatory markers. The follow-up time was 27 years, patient inclusion was strict, and there was a high degree of completeness of data collection and homogeneity. The SHAR is a validated data source with high completeness, including both public and private clinics performing THA in Sweden.(105) Both source populations are socioeconomically comparable to each other.

Limitations of studies III+IV

The samples were relatively small. The number of exclusions was high, as all patients had to attend a study visit and undergo CT scans to validate the exposure variable. Several cases may have been missed in the exclusion group, thus affecting the outcome. Patients who had undergone revision surgery were excluded without analysis prior to revision surgery. Including these patients would have increased the sample size as well as the risk of experiencing the primary outcome. Additionally, 3 patients were excluded due to pain in the hip, which could have been explained by loose components. Pre- or postoperative CVD could have been underreported or occurred in locations other than the greater Stockholm area, where the medical charts were out of reach. In patients who underwent bilateral hip replacement, only the first operated hip was included. There is the potential for an accumulated risk if both hips are replaced. Patients who died before screening might have

died from CVD, and the status of their hips regarding the presence of osteolysis is not known. From a clinical perspective, patients with a severe CVD burden and OA with indications for surgery may not undergo surgery because of the high perioperative risk. Patients were not stratified regarding the kind of PE used to make the liner. Until 2005, the liner used in these sample populations was made of conventional PE. The intention to introduce HXLPE was to decrease periprosthetic osteolysis related to PE wear, a large reason for THA revision. In fact, all our patients who had developed osteolysis (the cases) underwent surgery with standard PE, and none underwent surgery with HXLPE. During 2005, almost all cups implanted in Sweden were changed to HXLPE.

Many attempts have been made to classify osteolysis radiographically.(91, 92, 112-114) In this study, osteolysis was not stratified into subgroups, and the amount of wear of the liner was not assessed. Additionally, the femoral head size and type of stem were not taken into account. Smoking, BMI and the use of corticosteroids and statins were not assessed, which could have a potential influence on the development of periacetabular osteolysis and CVD. Statins are widely used to reduce cardiovascular morbidity and mortality, experimental studies have reported reduced osteoclast activity, and increased bone formation around implants.(115) The study population was largely white, and our findings may not be generalizable to more ethnically diverse populations. Despite the long and complete follow-up, the cohorts are relatively small and therefore the power of the analyses is limited. The follow-up time differed between the groups; it was significantly longer in the case group, which is a major limitation of this analysis, as the development of osteolysis, as well as CVD, is time-dependent.

GENERAL DISCUSSION

There is evidence showing that the initiation of OA is linked to vascular pathology.(116) Patients with OA may also have a higher risk of CVD.(117) The pathological features of CVD include arterial thickening, stiffness and atherosclerosis. These factors lead to deficient tissue perforation (ischaemia). The components of advanced OA are multiple ischaemia-induced bone infarcts and decreased cartilage nutrition. It is unclear whether there is an interaction or/and a causal relationship between OA and CVD. The prevalence of CVD increases with age, as over time, the heart and vasculature undergo alterations as a result of the deregulation of molecular longevity and often due to atherosclerotic disease. OA is also associated with ageing as a result of an age-related loss in the ability of cells and tissues to maintain homeostasis, particularly when placed under abnormal stress, such as biomechanical overloading of a joint. CVD and OA also have a possible common aetiology in chronic inflammation.(118, 119) There is a small increase in mortality 30 to 90 days postoperatively after THA.(120) Vascular disease has been reported as the most common cause of death among THA patients in general during this period and for up to four years after surgery.(121, 122) This is later followed by reduced mortality in THA patients up to 13 years post-operatively.(123, 124) The reduction changes with time into increased mortality and morbidity, mainly related to the cardiovascular system.(124) THA has also been associated with peripheral arterial disease on long-term follow-up.(125) The higher number of hospital admissions for THA patients due to cardiovascular reasons in the first two studies suggests an increased overall cardiovascular morbidity for these individuals. Peri-implant osteolysis and atherosclerosis have in common the condition currently suggested as long-term, ongoing, low-grade inflammation.(126, 127) This further strengthens the results from our cohort, where patients with later revision of the artificial joint suffered more cardiac events, and the mechanism for this finding can hence have several explanations. In studies 3 and 4, patients with asymptomatic periacetabular osteolysis were identified and investigated from a previously not studied point of view, at least to our knowledge, in a clinical setting. Contradictory to our assumptions from studies 1 and 2, no differences were found in either cardiovascular risk markers or levels of inflammatory markers, which opposes the hypothesis that higher levels of inflammation would be found in patients with osteolysis. The only disease with a borderline statistically significant difference between the groups was atrial fibrillation, which is strongly associated with inflammation.(110) The overall lack of differences does not exclude osteolysis as a possible risk factor for CVD, as shown in the register-based cohort studies. In contrast, the results could indicate that the presence of

osteolysis may have a relatively larger impact on the risk of CVD in the long term. Receptor activator of nuclear factor κ B (RANK), RANK ligand (RANKL), and osteoprotegerin (OPG) signaling pathway is responsible for the activation and differentiation of bone remodeling cells. Stimulation of the system is thought to be a possible trigger of periprosthetic osteolysis.(128) Further, vascular calcification is in part regulated by RANKL/RANK/OPG, and RANK proteins have been observed in atherosclerotic plaques.(129) The RANKL/RANK/OPG is considered as having equal importance in arterial calcification and osteolysis in bone (129) and may represent a common pathway in the pathology of OA, osteolysis and development of atherosclerosis.

CONCLUSIONS

- Patients with surgically treated OA of the hip may have an increased risk of cardiovascular morbidity and mortality many years after the operation. Patients who undergo THA and subsequent revision surgery due to loosening and/or osteolysis have a higher relative risk of developing cardiovascular events compared to controls. This observation may be indicative of common disease pathways, one of which could be triggered by local or systemic inflammatory activity.
- We found a higher rate of CVD in patients with periacetabular osteolysis than in patients with no osteolysis after THA. However, the difference was not statistically significant, and the longer follow-up of the patients with osteolysis makes the comparison difficult. Furthermore, we found no difference in cardiovascular risk markers between the groups.
- A larger sample size and more comparable length in time after surgery are recommended in future studies.

IMPLICATIONS FOR FUTURE STUDIES

This thesis provides one of the first assessments of the hypothesized association between asymptomatic periacetabular osteolysis and CVD. Insights gained from the studies may be of assistance to better understand the long-term effects of THA regarding cardiovascular mortality and morbidity. This understanding could help to improve future predictions of the long-term impact of THA. Further research is warranted in larger groups of patients with osteolysis, in patients treated with bilateral hip replacement, in patients treated with revision surgery for aseptic loosening/osteolysis, and in patients unable to undergo surgery due to risk factors regarding CVD burden. The approach would gain power if conducted as a multicentre study.

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